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Hydroxyl-Assisted Carbonylation of Alkenyltin Derivatives: Development and Application to a Formal Synthesis of Tubelactomicin A

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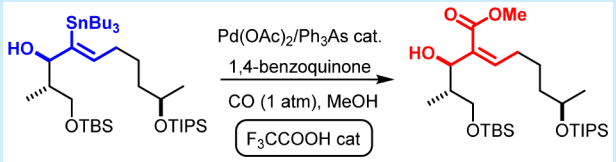
Supporting Information

ABSTRACT: Alkenyltin derivatives flanked by a hydroxyl group are subject to methoxycarbonylation when treated with catalytic amounts of $Pd(OAc)_2$ and Ph_3As in MeOH under a CO atmosphere; key to success is the use of 1,4-benzoquinone as a stoichiometric oxidant in combination with trifluoroacetic acid as a cocatalyst. The acid lowers the LUMO of the quinone and likely marshals the critical assembly of the substrates. Under the optimized conditions, competing proto-destannation is marginal; the method proved compatible with various (acid sensitive) functional groups and was applied to a short formal total synthesis of the antibiotic tubelactomicin A.



Recent work from this laboratory has shown that the hydrostannation of propargyl alcohol derivatives **A** with Bu_3SnH catalyzed by $[Cp^*RuCl]_4$ or $[Cp^*RuCl_2]_n$ is distinguished by remarkable levels of regio- and stereocontrol (Scheme 1).[1,2] The reaction follows an unusual *trans*-addition mode and faithfully delivers the tin residue to the proximal C atom of the reacting triple bond.[1] Experimental evidence suggests that this rewarding outcome originates from hydrogen bonding between the polarized [Ru−Cl] unit and the −OH group that locks the substrate within the coordination sphere of the catalyst, while an interligand interaction between the chloride and the incoming stannane predisposes the nucleophile for hydride delivery at the distal position;[1] in so doing, a loaded complex of type **B** evolves most likely via ruthenacyclopropene intermediates **B′** into the unorthodox *trans*-addition product **C**.[1,3]

The resulting structural motif **C** is highly useful, given the many opportunities that a C−Sn bond provides.[4] In a first foray, we explored cross-coupling with MeI, proto-destannation, or chloride-for-tin exchange; these reactions gave ready access to the antibiotic 5,6-dihydrocineromycin and synthetic analogues thereof.[5] Another potentially rewarding option is the conversion of **C** into trisubstituted enoates of type **D**, which are prevalent in nature (Scheme 1).

Although a two-step procedure comprising a tin/iodide exchange followed by carbonylation of the resulting alkenyl iodide allows products **D** to be reached, a direct methoxycarbonylation of **C** was deemed more attractive. Attempts at reducing this plan to practice, however, by reacting the model substrate **1** with methyl chloroformate under Stille conditions[6] were disappointing. Premature precipitation of palladium black and hence incomplete conversions, partial disproportionation of the chloroformate, and competing O-acylation and proto-destannation of the substrate were troublesome; even allene formation was observed in some runs.

Therefore, we turned our attention to a possible alkoxycarbonylation of alkenylstannanes of type **C**. While carbonylative Stille reactions with formation of ketones are well-known in the literature,[7] carbonylations with formation of carboxylic acid derivatives are exceedingly rare. The few recorded examples did not look overly promising either:[8] while some robust aryltin derivatives of type Ar_4Sn could be converted into the corresponding acid derivatives ArCOOH in modest yields, electron-rich substrates led to exclusive proto-destannation; the more common $ArSnBu_3$ derivatives solely afforded symmetrical ketones.[8] Moreover, the literature procedure uses $CuCl_2$ as an (over)stoichiometric oxidant, which is known to convert compounds of type **C** into the corresponding alkenyl chlorides.[5,9] Taken together, it seemed unlikely that this method applies to the projected case.

In the search for viable alternatives, we turned our attention to a recent report on the alkoxycarbonylation of arylboronates.[10] This procedure seemed attractive, as it employs catalytic $Pd(OAc)_2/PPh_3$ in combination with 1,4-benzoquinone as the oxidant and proceeds under essentially neutral conditions in MeOH (or other unhindered alcohols) as the solvent. Surprisingly though, all attempts at applying this method to stannane **1** failed completely, even at higher temperature (Table 1, entry 1). An extensive ligand screening did not improve the situation by much: although the use of $AsPh_3$[11] afforded small amounts of the desired product **2** (R = Me), the conversion remained invariably poor (entries 2, 3).

Since borane derivatives analogous to **1** amenable to carbonylation under the literature conditions[10] are currently not available by directed *trans*-hydroboration,[12] it was imperative to understand why alkenylstannanes are reluctant or even inert. We conjectured that the reoxidation of the Pd^0

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Scheme 1. Hydroxyl-Directed *trans*-Hydrostannation of Propargyl Alcohols Followed by Methoxycarbonylation; Representative Natural Products Featuring a Motif of Type D or an Immediate Derivative Thereof; • = CMe

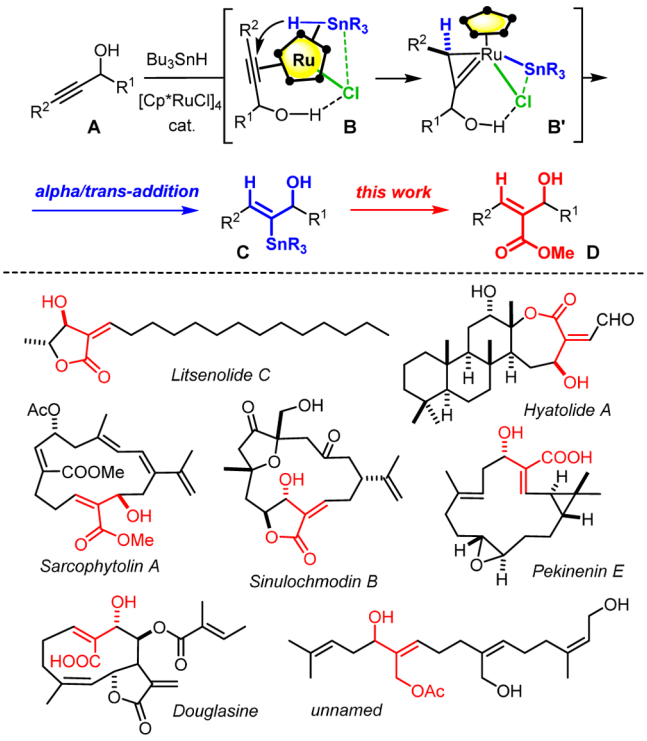
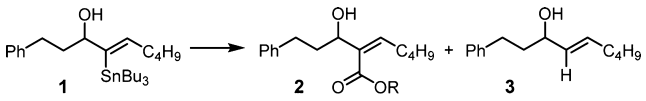


Table 1. Optimization of the Reaction Conditions for the Methoxycarbonylation of Stannane 1[a]

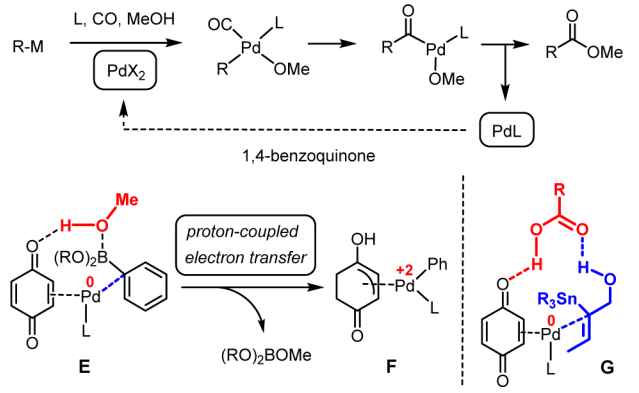


entry	ligand (mol %)	TFA (mol %)	temp (°C)	**1:2:3** (NMR)[b]
1	Ph_3P (12.5)	–	70	n.r.
2	Ph_3As (12.5)	–	70	61:39:0
3	Ph_3As (12.5)	–	20	84:16:0
4	Ph_3As (10)	20	20	50:50
5	Ph_3As (10)	50	20	0:83:17
6	Ph_3As (10)	**40**	**20**	**0:100:0**
7	Ph_3As (5)	40	20	14:86:0

[a]All reactions were performed with $Pd(OAc)_2$ (5 mol %) and 1,4-benzoquinone (1.5 equiv) under CO (1 atm) in MeOH. [b]Product distribution in the crude material as determined by ^1H NMR.

formed in the first turn of the catalytic cycle might be the culprit (Scheme 2). It has been shown in the past that protonation of the quinone carbonyl group is mandatory to ensure conversion of a [Pd^0·quinone] adduct into catalytically active Pd^{II} and hydroquinone.[13] Under the premise that only a proton-coupled electron transfer ensures efficient catalyst turnover, it seems reasonable that a Lewis acidic boron reagent has an inherent advantage over an organotin compound. By virtue of the empty p-orbital at boron, spontaneous coordination of MeOH used as the solvent will ensue;[10] the formation of an adduct of type **E** increases the Bronsted acidity of the alcohol and hence assists the crucial regeneration of Pd^{II} via protonation of the quinone (Scheme 2); at the same time, adduct formation will enhance the nucleophilicity of the

Scheme 2. (Top) Methoxycarbonylation of an Organometallic Substrate; (bottom) Rationale for the Privileged Reactivity of Arylboronates and Mechanistic Hypothesis How an Acid Cocatalyst Might Enhance the Reactivity of Stannanes Bearing Protic Functional Groups



organic residue to be transferred. Since organotin derivatives lack a similarly low-lying empty orbital, they are incapable of engaging in a similar assembly and are therefore obviously handicapped.

This shortcoming might be rectified by an acid cocatalyst, provided it does not lead to competing proto-destannation. It is tempting to speculate that a carboxylic acid would not only facilitate the necessary reoxidation of Pd^0 but also might play a more intricate role when working with substrates of type **C**: one can conceive a hydrogen bonding network of type **G** that fosters oxidative transmetalation by lowering the LUMO of the quinone, while ensuring the proximity of the reaction partners at the same time. The high affinity of palladium to the π-systems of the partners might partly compensate the entropic cost associated with this assembly, which mimics the proposed transition state **E** in the boron series.[10]

To test this hypothesis, our efforts focused on the use of trifluoroacetic acid (TFA) as a cocatalyst, which Bäckvall and co-workers had previously found to be a suitable partner for the Pd/quinone pair.[13,14] Indeed, addition of substoichiometric amounts of TFA boosted the methoxycarbonylation of compound **1**. A careful screening showed that the use of 40 mol % of TFA was optimal (Table 1, entry 6): lower concentrations led to incomplete conversions, while higher amounts resulted in substantial proto-destannation. Under these conditions, the reaction proved robust and scalable; even rather acid-sensitive functional groups passed uncompromised (Table 2). Not only were acetals, *tert*-alcohols, various silyl ethers, esters, and a nitrile found stable, but also two otherwise very sensitive, doubly allylic derivatives reacted without incident to give the corresponding products **7** and **8** in high yield. The data also show that the directing hydroxyl group can be primary, secondary, or tertiary, without much change in the efficiency of the reaction. The compatibility with unprotected hydroxyl groups is a distinct advantage over cross-coupling with chloroformates[15] and a desirable attribute in the quest for target-oriented syntheses that proceed with a minimum of protecting group manipulations. Particularly noteworthy is the compatibility of the method with an alkenyl bromide, which is prone to carbonylation in the presence of Pd^0; the fact that this group remained intact in product **10** suggests that reoxidation to Pd^{II} by the 1,4-benzoquinone/TFA couple is fast enough to outperform oxidative addition of Pd^0 into the C–Br bond.

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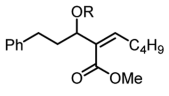
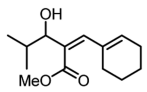
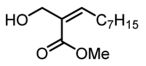
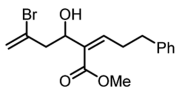
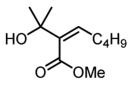
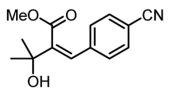
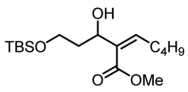
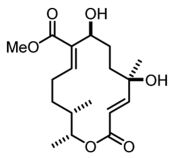
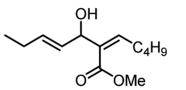
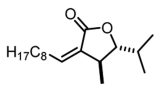
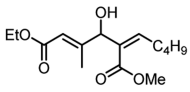
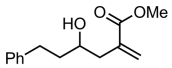
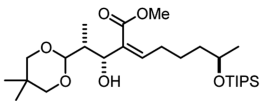
Table 2. Scope of the Methoxycarbonylation of Alkenylstannanes Flanked by Hydroxyl Groups[a]

product	yield (%)	product	yield (%)
	**2a**: 86 (R = H) **2b**: 0 (R = MOM) **2c**: 0 (R = TBS)		**9**: 55[b]
	**4**: 68		**10**: 87
	**5**: 63		**11**: 75[b]
	**6**: 77[b]		**12**: 69
	**7**: 72		**13**: 60
	**8**: 80[b]		**14**: decomp.
			**15**: 87[b]

[a]Unless stated otherwise, all reactions were carried out with $Pd(OAc)_2$ (5 mol %), Ph_3As (10 mol %), TFA (40 mol %), and 1,4-benzoquinone (1.5 equiv) in MeOH under CO (1 atm) at 20 °C. [b]At 45 °C.

Macrolide **12**, formed by methoxycarbonylation, is an analogue of 5,6-dihydrocineromycin B and hence extends the small library of non-natural analogues of this antibiotic previously made by late-stage modification of the very same advanced organotin intermediate.[5] The ready formation of product **13** proves that homoallylic tin derivatives are carbonylated with spontaneous formation of a densely functionalized α-alkylidene-γ-butyrolactone ring, a substructure found in a myriad of bioactive natural products. The generality of this transformation, however, needs to be explored in more detail, since an analogous stannane with a terminal C═C bond failed to afford compound **14**.

Of mechanistic interest is the fact that the protection of the −OH group in the model substrate **1** as MOM acetal or TBS ether did not allow the methoxycarbonylation to proceed (see products **2b**,**c**). Likewise, alkenylstannanes devoid of an allylic −OH group do not behave well but rather get decomposed. Therefore, it is reasonable to assume that the acid additive does not merely assist the reoxidation of the catalyst but likely marshals the reaction partners via hydrogen bonding and, in so doing, assists the surmised proton shuttle in the decisive step of the catalytic cycle.[16]

The significance of the new method is further illustrated by an application to the formal total synthesis of (+)-tubelactomicin A.[17] This macrolide antibiotic has attracted considerable attention in the past for its unique and challenging structure as well as for its potent and specific antimicrobial activities against various types of mycobacteria, including several drug-resistant strains.[17−19]

One of the reported total syntheses assembles the target from the decalin building block **17** and the acyclic derivative **16**, which was prepared in 25 steps starting from methyl lactate (Figure 1).[18a,19] We saw an opportunity to streamline the route

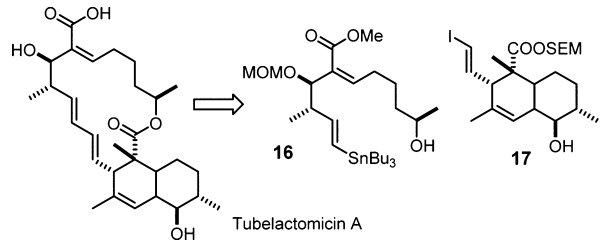
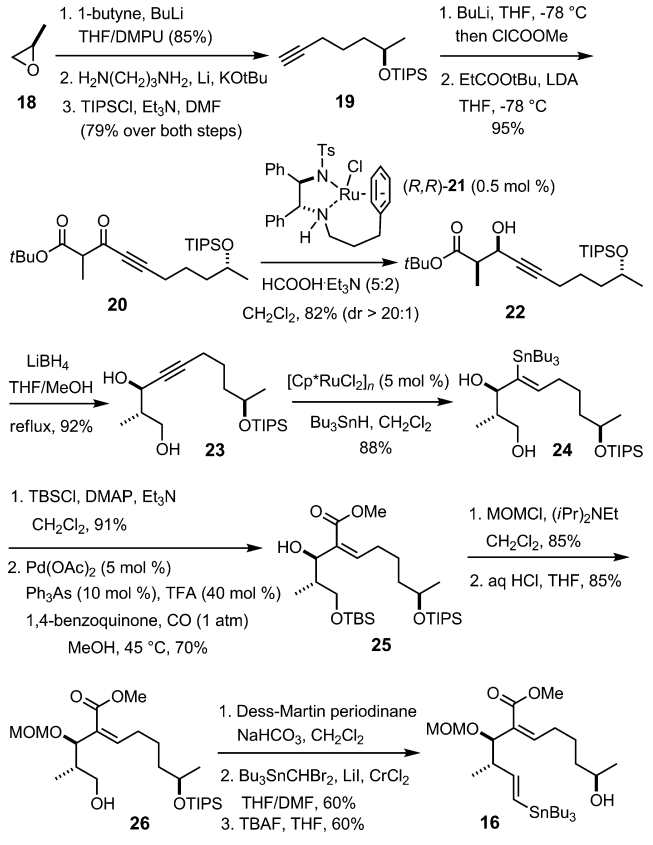


Figure 1. Retrosynthetic analysis of the antibiotic tubelactomicin A reported in ref 18a.

to this particular fragment with the aid of the new method. To this end, commercial epoxide (*R*)-**18** was opened with lithiated 1-butyne, and the resulting product was subjected to the alkyne zipper reaction to shift the triple bond to the terminus (Scheme 3).[20] Standard O-silylation followed by C-acylation of **19** with

Scheme 3. Formal Total Synthesis of Tubelactomicin A



methyl chloroformate gave the corresponding ester, which was subjected to a Claisen condensation to give compound **20** in high overall yield. A kinetic dynamic resolution under transfer hydrogenation conditions using complex **21** as a precatalyst worked well on scale to form the *syn*-aldol motif of **22** with excellent diastereoselectivity (dr >20:1).[21] Reduction of the ester set the stage for the key *trans*-hydrostannation catalyzed

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by $[Cp^*RuCl_2]_n$:[1] as expected, the directing effect of the free −OH group flanking the triple bond in **23** could be harnessed, and product **24** be isolated as a single regio- and stereoisomer in 88% yield on a >3 g scale.

The methoxycarbonylation of the silyl ether derived from **24** also proceeded nicely to furnish the required trisubstituted enoate **25** in good yield. In order to exactly match fragment **16** previously used in the literature,[18,19] **25** had to be elaborated in a stepwise manner, which proceeded uneventfully, including the final Takai-type olefination with formation of the terminal alkenylstannane moiety.[22,23] With only 14 steps, this approach to compound **16** is considerably shorter than the existing route (25 steps)[18a,19] and relies on the power of homogeneous catalysis in its key steps. We like to emphasize that the sequence could be shortened by several more steps if one were to accept a slightly different protecting group pattern, which would, almost certainly, also allow tubelactomicin A to be reached in the end.

In any case, we are confident that the conceptually new and exceedingly mild approach to trisubstituted enoates described herein based on a hydroxyl-directed *trans*-hydrostannation followed by methoxycarbonylation is highly enabling, in view of the many natural products that comprise this particular structural element or a derivative thereof.[24] Further efforts to showcase this notion will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01431.

Experimental procedures, compound characterization data and copies of spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(12) Hydroxyl-directed *trans*-hydroboration of propargyl alcohol derivatives is currently not possible because pinacol borane reacts faster with the −OH group than with the triple bond; for *trans*-hydroboration of other internal alkynes, see: Sundararaju, B.; Fürstner, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 14050.

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(15) The synthesis described in ref 6c shows that a lateral *sec*-OH group has to be protected prior to the cross-coupling of an alkenylstannane moiety with methyl chloroformate.

(16) Alternatively, one might assume that the −OH group of the substrate reacts with $[L_2Pd(tfa)_2]$ to give a transient complex of type $[L_2Pd(tfa)(O{-}CHR{-}C(SnBu_3){=}CHR)]$, which undergoes an intramolecular palladium-for-tin exchange via a four-membered transition state; control experiments with overstoichiometric $Pd(tfa)_2$ and Ph_3As in the absence of 1,4-benzoquinone render this explanation unlikely: the reactions were messy and led to rapid palladium precipitation; protodestannation largely prevailed over carbonylation.

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